Pergamon

TETRAHEDRON

Tetrahedron 57 (2001) 6463–6473

Practical stereoselective synthesis of conformationally constrained unnatural proline-based amino acids and peptidomimetics

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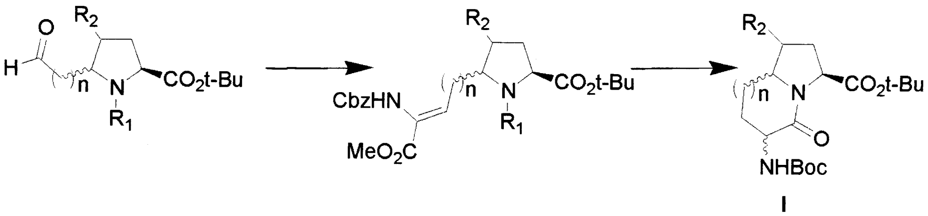
Received 5 February 2001; revised 6 March 2001; accepted 22 March 2001

Abstract—A practical synthetic scheme was developed to prepare both the *cis*- and *trans*-fused stereoisomers of *N*-Boc-L-octahydroindole-2-carboxylic acid (L-Oic) methyl ester. Key event of the synthetic sequence was the ring-closing metathesis of a suitable diallylated proline derivative. This is the first reported practical synthesis of the *trans*-fused isomer. Functionalization of the octahydroindole nucleus by electrochemical oxidation followed by acid-catalysed allylation paved the way for the preparation of reverse-turn dipeptide mimics. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Biologically active peptides are involved in a great number of physiological processes through their interaction with receptors and enzymes. However, peptides are not ideal drug candidates due to their low metabolic stability toward endogenous proteases, poor oral bioavailability, rapid excretion, and lack of selectivity towards a specific receptor, due to conformational flexibility. These difficulties could be overcome by resorting to peptide analogues or *de novo*-designed molecules that mimic the bioactive conformation and the action of the native peptides at the receptor level. These molecules, called peptidomimetics, should display high receptor affinity and selectivity, in addition to enhanced bioavailability and metabolic stability. In the field of peptidomimetics much effort has been focused on the design and synthesis of conformationally constrained compounds that mimic or induce certain secondary structural features of peptides and proteins.[1]

Since reverse-turn motifs are implicated as recognition elements in a variety of biological interactions, the design of small constrained mimetics of turn structures is of great importance to medicinal chemistry. This goal has been frequently achieved by replacing reverse-turn dipeptide motifs with constrained molecules that reproduce their conformational features. In that regard, a particularly attractive class of compounds are fused bicyclic systems,[2] and in particular the 1-aza-2-oxobicyclo[X.Y.0]alkane amino acids. Owing to their rigid geometry, these scaffolds are also useful tools to probe and elucidate structure–activity relationships.



Scheme 1. Synthetic scheme leading to 1-aza-2-oxobicyclo[X.3.0]alkane amino acids of general formula I.

Keywords: ring-closing metathesis; unnatural amino acids; octahydroindole ring; peptidomimetics.

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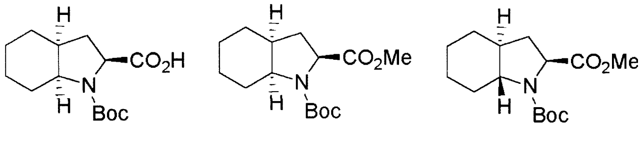
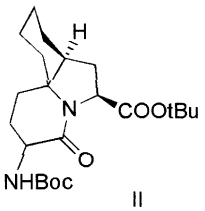
PII: S0040-4020(01)00538-5



1 **2** **3**

Figure 1. Commercially available octahydroindole-2-carboxylic acid derivatives **1** and **2** and the *trans* isomer **3**.



II

Figure 2. Trinuclear dipeptide mimics of general formula II.

In the course of our studies on peptide secondary structure mimics, we have synthesized several 5,5- 6,5-, 7,5- and 8,5-fused 1-aza-2-oxobicyclo[X.3.0]alkane amino acids (Scheme 1, general formula I),[3] that can be regarded as conformationally restricted substitutes for X-Pro dipeptide units. All these bicyclic lactams include a natural L-Pro residue, but vary in the lactam ring size, and in the configuration at the fusion carbon atom and at the NH_2-bearing carbon. The conformational properties of these proline-derived bicyclic lactams have been investigated by a combination of computational and spectroscopic techniques, to assess their propensities to mimic the reverse-turn peptide motif.[4] These studies have revealed that these bicyclic scaffolds can mimic reverse-turn motifs, although there is a dependence of the turn-inducing ability on lactam ring size and stereochemistry. Reverse-turn mimetic bicyclic lactams have been shown to exhibit a tendency to form an inverse γ-turn or a type II′ β-turn.

The possibility of functionalizing these molecules with lipophilic appendages is very attractive because they could improve peptide-receptor affinity by interacting with hydrophobic pockets. To this end, commercially available unnatural amino acid *N*-Boc-L-octahydroindole-2-carboxylic acid (*N*-Boc-L-Oic) **1** (Fig. 1) was recognized as a different, suitable starting point for azabicycloalkane synthesis. Substitution of hydrophobic residues in critical regions of biologically active peptides by this conformationally constrained, proline-based unusual amino acid has been proved to be successful in mapping the unknown topology of peptide receptors and in developing potent receptor antagonists. For example, a number of bradykinin B_2 receptor antagonists have been reported that contain nonproteinogenic amino acid pair X-L-Oic, forcing a β-turn into the backbone when positioned, respectively, at the $i+1$ and $i+2$ positions of the turn.[5] However, the high cost of this amino acid, its relevance in the synthesis of bioactive compounds and the availability of only one isomer convinced us to investigate a synthetic sequence, which could start from inexpensive and commercially available products, to synthesize different stereoisomers of octahydroindole derivatives.

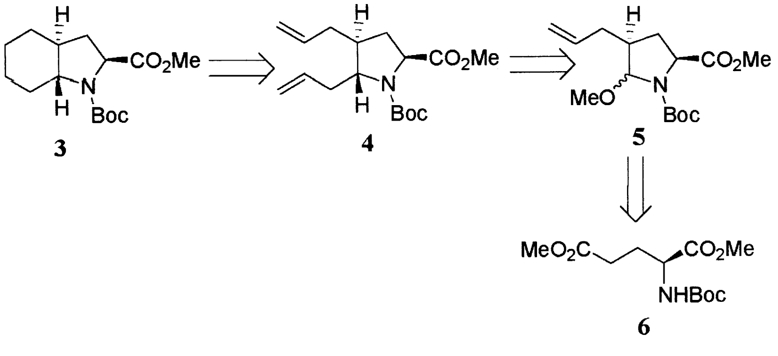
In this paper, we report on a convenient method for the synthesis of both *cis*- and *trans*-fused stereoisomers of *N*-Boc-L-octahydroindole-2-carboxylic acid methyl ester **2** and **3** (Fig. 1), which could be inserted as sterically restricted unnatural residues in biologically active sequences to study both structural and biological properties.

Functionalization of the octahydroindole nucleus by electrochemical oxidation and its conversion into reverse-turn dipeptide mimics of general formula II (Fig. 2) is also described in the paper.

2. Results and discussion

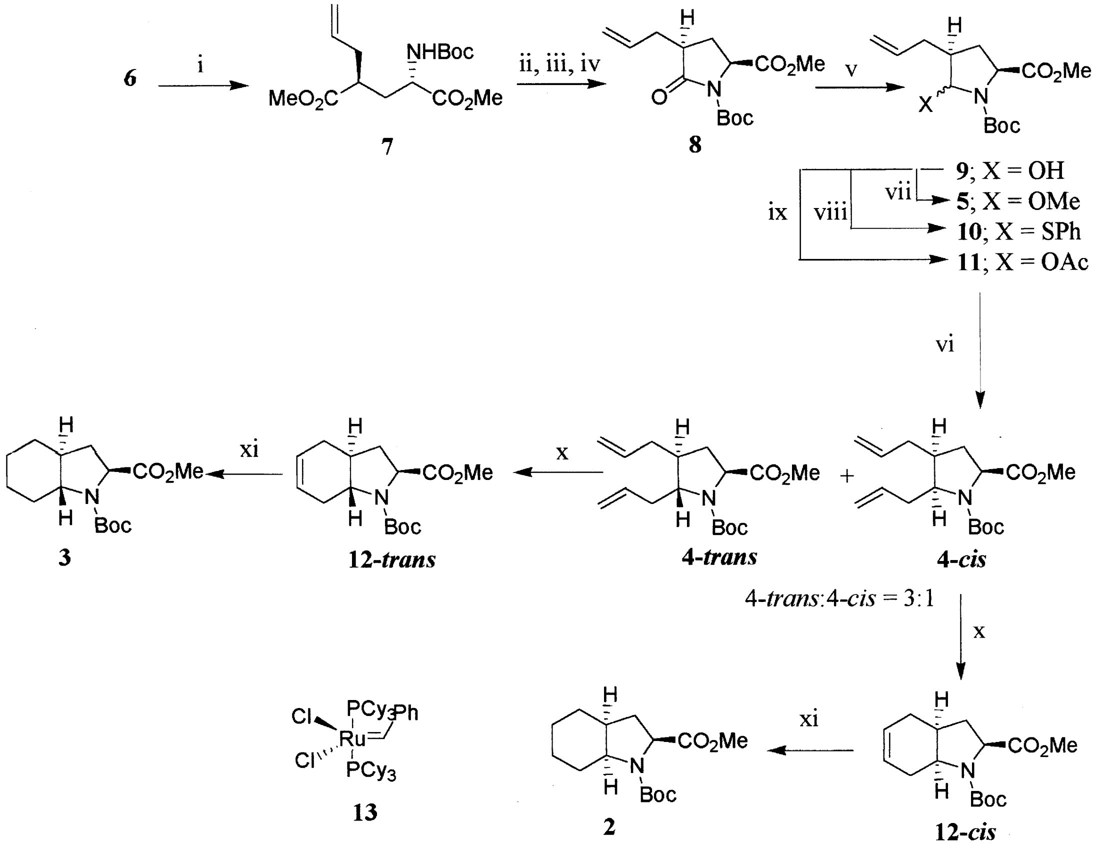
The current literature methods for obtaining 2-carboxyoctahydroindole derivatives are based on the use of tyrosine compounds as starting materials.[6] Although *cis*-fused octahydroindol-6-one derivatives are achievable in multigram amounts and good yields, the *trans*-fused stereoisomers are not attainable by the same methodology. As mentioned above one stereoisomer of *N*-Boc-L-octahydroindole-2-carboxylic acid (*N*-Boc-L-Oic) **1** is commercially available but its ring junction is *cis* as well (Fig. 1).

Therefore the synthesis of *trans*-fused derivatives could be of significant interest, both because of the challenge inherent with the stereoselective formation of the *trans* junction, and because such compounds, when inserted into peptide chains, may induce conformational patterns different from those originated by the *cis* counterparts. Here we report on a method for the stereoselective synthesis of



3 **4** **5** **6**

Scheme 2. Retrosynthetic analysis of compound **3**.



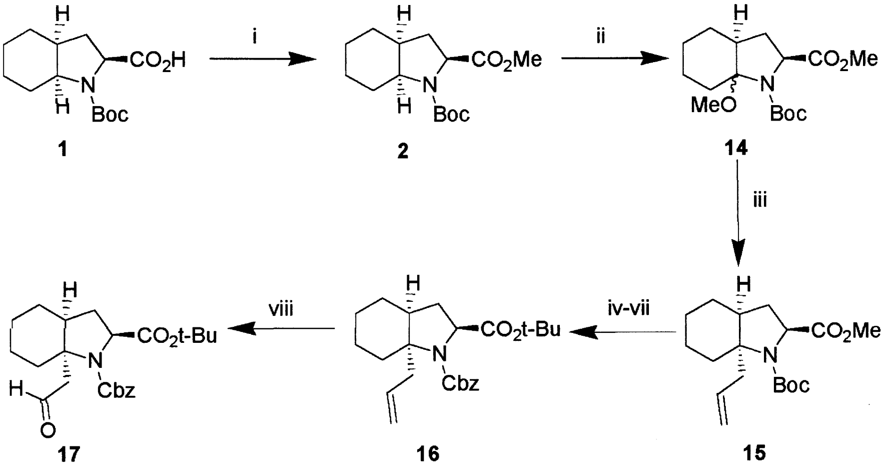
Scheme 3. i: HMDS, BuLi, allyl bromide, THF, 72%; ii: TFA, CH_2Cl_2, 0°C; iii: toluene, 110°C, 85% over two steps; iv: Boc_2O, DMAP, THF, 98%; v: $LiEt_3BH$, THF, -78°C, 91%; vi: Allyl tributyltin, *tert*-butyldimethylsilyl trifluoromethanesulphonate, -78°C, 75%; x: Grubbs catalyst, CH_2Cl_2, 91%; xi: H_2, Pd/C, EtOH, 95%.

the unknown *trans*-fused *N*-Boc-L-octahydroindole-2-carboxylic acid methyl ester (*N*-Boc-L-Oic-OMe) **3**. The retrosynthetic analysis of **3** is depicted in Scheme 2. The key events for the synthesis are the ring-closing metathesis of the diallylated proline derivative **4** and the allylation of the *N*-acyliminium ion derived from the hemiaminal **5**. Nucleophilic addition of the allyl unit could be anticipated to occur predominantly on the opposite side of the adjacent allyl substituent thus providing the desired 4,5-*trans* diallyl derivative **4**.

The starting material for the synthesis was the *N*-Boc-protected dimethyl glutamate **6**, which was converted into the 4-allyl pyroglutamic ester **8** following a four-step synthetic pathway reported in a recent communication,[7] and summarized in Scheme 3.

Treatment of the Li-enolate of **6** with allyl bromide afforded the 4-(*S*)-allyl derivative **7** in good yield and almost complete stereoselectivity (>98:2). This, in turn, was *N*-deprotected with trifluoroacetic acid and thermally cyclized to the corresponding pyroglutamate. Reprotection of the lactam as an *N*-Boc derivative using standard conditions led to the pyroglutamate **8**. Attempts to shorten the synthetic sequence by directly cyclizing the *N*-carbamate anion of **7**, thus avoiding the deprotection and reprotection steps, gave unsatisfactory results.

Selective reduction of the imide **8** to the hemiaminal **9** was best performed by the use of lithium triethylborohydride at -78°C. According to ample literature precedent and our own experience on similar substrates,[8] hemiaminal **9** was first converted to the corresponding methoxy derivative **5**, which should be a more suitable substrate for the following acid-catalysed allylation reaction. Brief treatment of **9** with a methanol solution of excess trimethyl orthoformate in the presence of catalytic pyridinium tosylate gave **5** in 94%. However, despite several attempts using either allyltributyltin or allyltrimethylsilane in the presence of various Lewis acids, in all cases the allylated product **4** was formed in unacceptably low yields. Suspecting that the scarce reactivity of the methoxylated substrate was to ascribe primarily to the inefficient formation of the intermediate *N*-acyliminium ion, we tried to raise the reaction rate by switching to a better leaving group. Support for this hypothesis came from the behaviour of the thiophenyl derivative **10**, which did not react at all, the sulfide moiety being a poor leaving group. In contrast, replacement of the methoxy by an acetoxy substituent was shown to be particularly beneficial in the subsequent allylation reaction. The best yielding conditions required a twofold excess of allyltributyltin and *tert*-butyldimethylsilyl trifluoromethanesulphonate. Eventually we discovered that the aminal **9** itself could be allylated in the same conditions and almost the same yield as the acetoxy derivative **11**, thus making the synthetic sequence one step shorter. The diallyl product was obtained as a mixture of *trans* and *cis* isomers **4-*trans*** and **4-*cis*** in a 3:1 ratio, as determined by NMR analysis of the crude



Scheme 4. i: CH_3I, $KHCO_3$, DMF, 99%; ii: anodic oxidation, Me_4NBF_4, $NaHCO_3$, CH_3CN, MeOH, 84%; iii: allyltributyltin, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78°C, 97%; iv: TFA, CH_2Cl_2, 89%; v: $KHCO_3$, benzyl chloroformiate, EtOAc/H_2O 1:1, 99%; vi: LiOH, dioxane, 50°C, 100%; vii: *N*,*N*-dimethylformamide di-*tert*-butyl acetal, benzene, 92%; viii: $OsCl_3$, $Me_3NO{\cdot}2H_2O$, acetone/H_2O 8:1, $NaIO_4$, 93%.

reaction mixture and also by the relative mass balance of the pure isomers isolated by flash chromatography. Configurational assignments were postponed to the achievement of the final products whose comparison with *N*-Boc-L-Oic-OMe **2** will give an immediate answer to their stereochemical identity.

The ring-closing metathesis of the separate stereoisomers **4-*trans*** and **4-*cis*** proceeded uneventfully in less than a hour at room temperature by the action of 10% of the Grubbs catalyst[9] **13** (>90% yield). The resulting olefins **12-*trans*** and **12-*cis*** were hydrogenated with 5% Pd on charcoal affording the final stereoisomeric product **3** and **2**, respectively. Comparison of spectroscopic data (IR, ^{1}H and ^{13}C NMR) between our final compounds and the methylester **2**, derived from commercial *N*-Boc-L-Oic-OH **1** (Scheme 4), showed unequivocally their stereochemical patterns as those indicated in Scheme 3.

The protocol we have developed for the construction of proline-based bicyclic lactam dipeptide mimics[3e] (Scheme 1) is based on a Horner–Emmons olefination on a suitably protected aldehyde followed by double-bond reduction and cyclization. In order to exploit the octahydroindole nucleus in this sequence for the synthesis of dipeptide mimics II (Fig. 2), functionalization of Oic by electrochemical oxidation[10] of **2** and **3** was attempted. These studies revealed that the *trans* isomer **3** gives, under the standard conditions used for proline, a mixture of methoxylated regioisomers in low yields. In contrast, compound **2** can be regioselectively methoxylated by electrochemical oxidation in CH_3CN/MeOH to give a mixture of stereoisomeric 7a-methoxy-octahydroindole derivatives **14** in 84% yield (Scheme 4). From **14** the required aldehyde **17** was obtained as described in Scheme 4. Thus, compound **14** was submitted to allylation with allyltributyltin in the presence of an appropriate Lewis acid ($BF_3{\cdot}Et_2O$, 97%) in anhydrous CH_2Cl_2 affording compound **15** as the only isomer. Proline allylation via *N*-acyl iminium ion has been studied intensively,[8] and found to occur with modest selectivity (typically 3:1) in favour of the *cis* isomer. The much higher selectivity observed in the allylation of **14** could be rationalized by taking into account the conformation of the intermediate *N*-acyl iminium ion, which was calculated by molecular mechanics.[11] Inspection of the structure shown in Fig. 3 reveals that the ion should adopt a concave shape that should preclude nucleophilic attack from the β face. However, one must be aware of the inadequacy of drawing stereochemical conclusions on the course of a reaction from the molecular mechanics ground state conformation of a charged intermediate. In any case, the stereochemistry of the newly formed stereocentre was determined by NOE experiments. The *cis*-fusion arrangement was evidenced by the presence of NOEs between the allylic moiety protons and H-3a, as shown in Fig. 4. Absence of epimerization at the other stereogenic centres during allylation was

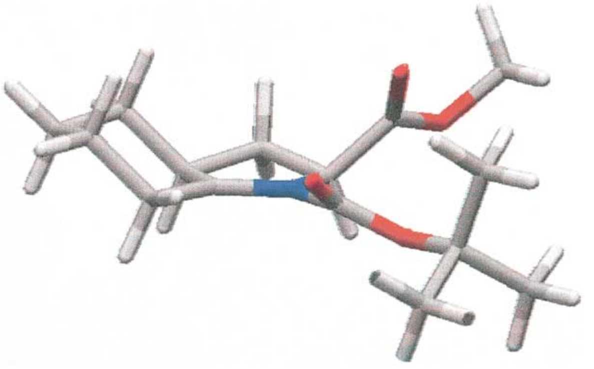


Figure 3. Molecular mechanics conformer (AMBER* force field) of the intermediate *N*-acyl iminium ion leading to **15**.

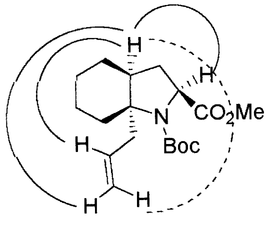
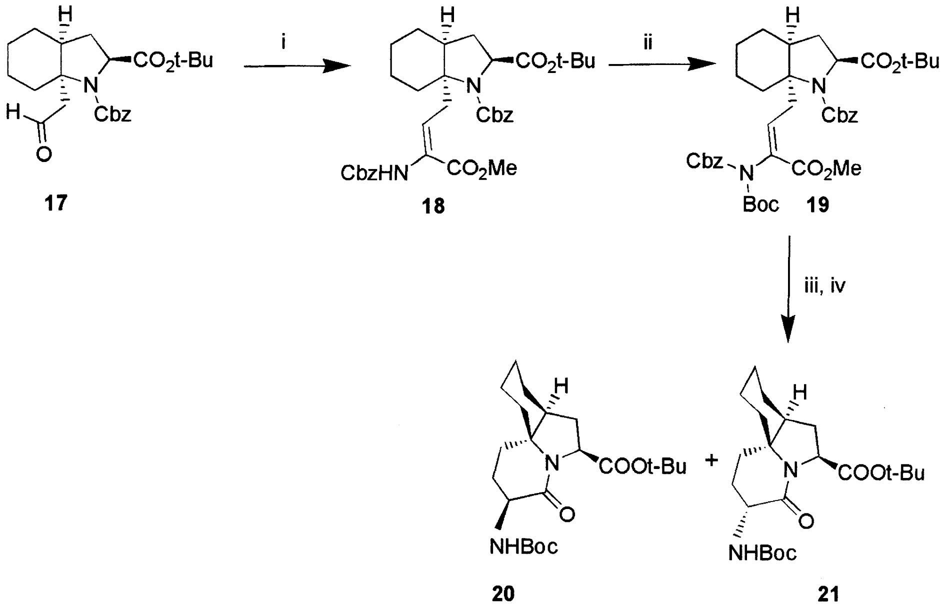


Figure 4. NOE contacts observed for compound **15**.



Scheme 5. i: Z-(α)-phosphonoglycine trimethyl ester, tBuOK, CH_2Cl_2, −78°C, 85%; ii: Boc_2O, DMAP, THF, 88%; iii: H_2, Pd/C 10%, MeOH; iv: toluene, reflux, 85% over two steps.

confirmed by NOE between H-2 and H-3a. Compound **16** was obtained from **15** by protecting group manipulation, which consists of an exchange of —*N*-Boc with —*N*-Cbz and —COOMe with —COO*t*-Bu. These transformations were performed with the aim of preparing orthogonally protected intermediates. Deprotection of the *N*-Boc group of **15** with TFA followed by *N*-Cbz reprotection gave the benzyloxycarbonyl derivative, which was hydrolysed to the corresponding carboxylic acid and subsequently treated with dimethylformamide di-*t*-butylacetal affording the suitably protected compound **16** in 81% overall yield over four steps. Dihydroxylation of **16** with $OsCl_3$, Me_3NO in 8:1 acetone/water, followed by $NaIO_4$ cleavage of the intermediate diols gave the aldehyde **17** in 93% yield.

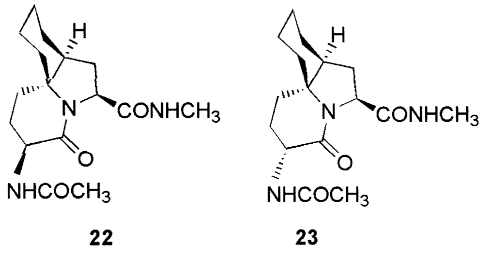


Figure 5. Dipeptide mimics **22** and **23** used in computer modelling.

Horner–Emmons olefination of **17** with the potassium enolate of (±)-Z-α-phosphonoglycine trimethyl ester[12] (Scheme 5) set up the complete framework of the final product in 85% yield. Treatment of **18** with Boc_2O and subsequent unselective hydrogenation of the protected

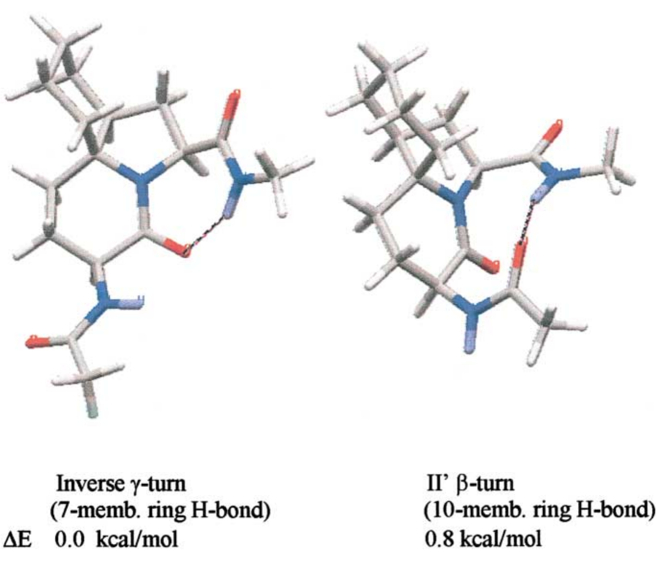


Figure 6. Low-energy conformers (AMBER* force field) calculated for dipeptide mimic **22**.

compound **19** (H_2, Pd/C) followed by refluxing in toluene gave a 1:1 mixture of easily separable **20** and **21**.[13]

Computational studies designed to investigate the ability of the newly synthesized dipeptide mimics to adopt reverse-turn conformations were performed on the model compounds **22** and **23** (Fig. 5), following the protocol previously employed in the study of other azabicycloalkane amino acids.[4,11] Monte Carlo molecular mechanics conformational searches revealed that only mimic **22**, having the carboxy and the amino groups on the same face of the bicyclic system, is an effective turn-inducer, promoting either an inverse γ-turn or a type II′ β-turn through intramolecular hydrogen bonding. The only two conformers calculated in vacuo for compound **22** within 2 kcal/mol of the global minimum are given in Fig. 6.

In summary, we have reported a convenient synthetic route for the preparation of a novel, conformationally constrained, unnatural amino acid, the *trans*-fused *N*-Boc-L-octahydroindole-2-carboxylic acid methyl ester **3**. By the same sequence the *cis*-fused L-Oic derivative **2** can also be obtained, although as the minor stereoisomer. This is the first known synthesis of the *trans* L-Oic and it will allow studying the effect of this residue on both the structural and biological properties of bioactive peptides. Regioselective functionalization of the octahydroindole nucleus has been successfully performed on the *cis*-fused isomer by an electrochemical oxidation reaction that occurs selectively at the 7a position. The 7a-methoxy derivative allowed the synthesis of novel trinuclear dipeptide mimics, which may improve peptide-receptor affinity by interacting with hydrophobic pockets.

3. Experimental

3.1. General

Proton NMR spectra were recorded on Bruker AC-200 or AC-300 spectrometers. Proton chemical shifts are reported in parts per million (ppm) relative to internal tetramethylsilane and the coupling costants in hertz (the usual abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet). Carbon NMR spectra were recorded on Bruker AC-200 (50.3 MHz) or AC-300 (75.4 MHz) spectrometers; carbon chemical shifts are reported in ppm relative to TMS. NMR data were collected at 300 K, unless otherwise indicated. Elemental analyses were performed with a Perkin–Elmer 240 instrument. Mass spectra were obtained with a VG 7070 EQ spectrometer. Melting points were determined on a Stuart Scientific SMP3 melting point apparatus. Optical rotations were measured in 1 dm pathlength cells of 1 ml capacity by using a Perkin–Elmer 241 polarimeter. Thin-layer chromatography (TLC) was carried out using Merck precoated silica gel F-254 plates. Flash chromatography was carried out with Macherey–Nagel Silica Gel 60, 230–400 mesh. Solvents were dried using standard procedures and reactions requiring anhydrous conditions were performed under an argon or nitrogen atmosphere.

3.1.1. (2*S*,4*S*)-2-Allyl-4-*tert*-butoxycarbonylamino-pentanedioic acid dimethyl ester (7). A solution of hexamethyldisilazane (3.96 ml, 17.50 mmol) in dry THF (17 ml) under nitrogen was treated with *n*-butyllithium (1.6 M solution in *n*-hexane, 10.9 ml) at 0°C for 10 min. After cooling to −78°C, a solution of **6** (2302 mg, 8.36 mmol) in dry THF (33 ml) was added dropwise by syringe and the resulting pale yellow solution stirred at the same temperature for 45 min. Then freshly distilled allyl bromide was added and the reaction mixture stirred for 3.5 h. A 10% HCl aqueous solution (10 ml), saturated brine (20 ml) and Et_2O (50 ml) were added, and the aqueous phase extracted with 2×30 ml of Et_2O. The organic layers were collected, dried with Na_2SO_4 and evaporated to dryness giving an oily residue that was flash chromatographed (hexanes/EtOAc 7:3) to afford **7** (1906 mg, 6.05 mmol, 72%) as a colourless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.95–2.04 (m, 2H), 2.34 (m, 2H), 2.58 (quintet, J=6.9 Hz, 1H), 3.67 (s, 3H), 3.73 (s, 3H), 4.35 (ddd, J_1=J_2=7.8 Hz, 1H), 4.96 (d, J=7.8 Hz, 1H), 5.02–5.13 (m, 2H), 5.63–5.78 (m, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 28.2, 34.6, 37.3, 42.7, 52.6, 53.0, 53.3, 80.9, 118.6, 135.3, 156.3, 173.7, 176.4; IR (liquid film) 3370, 1737, 1511, 1367, 1168, 1050, 919 cm^{-1}; Elemental analysis for $C_{15}H_{25}NO_6$: Calculated: C, 57.13; H, 7.99; N, 4.44; Found: C, 57.24; H, 8.00; N, 4.43; MS: *m/e* (rel. intensity): 316 (1), 256 (18), 228 (3), 215 (7), 200 (38), 184 (15), 168 (7),156 (75), 139 (4), 124 (25), 114 (3), 96 (17), 82 (9), 67 (3), 57 (100).

3.1.2. (2*S*,4*S*)-4-Allyl-5-oxopyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (8). TFA (7 ml) was added under nitrogen to a solution of **7** (2580 mg, 8.19 mmol) in CH_2Cl_2 at 0°C and the resulting pale yellow solution stirred at the same temperature for 90 min. After evaporation to dryness, the oily light brown residue was treated with aqueous Na_2CO_3 and extracted with EtOAc (3×20 ml). TLC analysis showed the presence of only one spot (R_f 0.52, AcOEt/MeOH 95:5). After drying and evaporation of the solvent TLC analysis showed that part of the product was converted into a new compound (R_f 0.55, AcOEt/MeOH 95:5) that was recognized as the cyclized product. To complete the cyclization the crude reaction mixture was dissolved in toluene (35 ml) and heated at 110°C for 40 min. Evaporation of the solvent and purification by flash chromatography (EtOAc) gave 4-allyl-5-oxopyrrolidine-2-carboxylic acid *tert*-butyl ester as a colourless oil (1273 mg, 85%). ^1H NMR (300 MHz, $CDCl_3$) δ 1.17–1.93 (m, 1H), 2.06–2.21 (m, 1H), 2.46–2.63 (m, 3H), 3.74 (s, 3H), 4.19 (t, J=7.8 Hz, 1H), 5.00–5.03 (m, 1H), 5.03–5.09 (m, 1H), 5.65–5.80 (m, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 30.2, 34.8, 40.5, 52.3, 53.6, 117.0, 134.8, 172.2, 178.4; IR (liquid film) 3240, 1744, 1706, 1382, 1217, 1116, 1024, 921 cm^{-1}; Elemental analysis for $C_9H_{13}NO_3$: Calculated: C, 59.00; H, 7.15; N, 7.65; Found: C, 59.12; H, 7.16; N, 7.64; MS: *m/e* (rel. intensity) 183 (13), 182 (40), 153 (1), 124 (100), 106 (3), 96 (41), 81 (45), 67 (7), 59 (13), 55 (10), 41 (17).

Di-*tert*-butyl dicarbonate (1880 mg, 8.60 mmol) and DMAP (30 mg) were added to a solution of 4-allyl-5-oxopyrrolidine-2-carboxylic acid *tert*-butyl ester (1200 mg, 6.55 mmol) in distilled THF (20 ml) at room temperature. After stirring for 120 min, the solvent was evaporated to dryness and the crude oily product flash chromatographed (hexanes/EtOAc 7:3) to give **8** (1820 mg, 98%) as colourless needles. Mp: 54–56°C (*n*-pentane–Et$_2$O); ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.50 (s, 9H), 1.73 (ddd, J=6.9 Hz, J=6.9 Hz, J=13.7 Hz, 1H), 2.15–2.29 (m, 1H), 2.48 (ddd, J=8.7 Hz, J=8.7 Hz, J=13.7, 1H), 2.59–2.70 (m, 2H), 3.78 (s, 3H), 4.51 (dd, J=8.7 Hz, J=7 Hz, 1H), 5.03–5.08 (m, 1H), 5.09–5.11 (m, 1H), 5.66–5.82 (m, 1H); ^{13}C NMR (75.4 MHz, CDCl$_3$) δ 26.5, 27.7, 34.8, 41.8, 52.2, 57.1, 83.4, 117.5, 134.3, 149.0, 171.8, 174.1; IR (nujol) 1773, 1741, 1335, 1310, 1286, 1258, 1200, 1185, 1124, 1051, 997, 961, 915, 788 (cm^{-1}); Elemental analysis for C$_{14}$H$_{21}$NO$_5$: Calculated: C, 59.35; H, 7.47; N, 4.94; Found: C, 59.29; H, 7.48; N, 4.95; MS, *m/e* (rel. intensity) 283 (39), 196 (4), 183 (53), 168 (15), 124 (100), 115 (1), 96 (4), 81 (13), 67 (3), 57 (82).

3.1.3. (2*S*,4*S*,5*S*) and (2*S*,4*S*,5*R*)-4,5-Diallyl-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (4-*cis*, 4-*trans*). A 1 M solution of lithium triethylborohydride in THF (6.60 ml, 6.60 mmol) was added dropwise by syringe to a dry THF solution (30 ml) of **8** (1703 mg, 6.01 mmol) under nitrogen at −78°C. After stirring for 60 min, a saturated NH$_4$Cl solution and Et$_2$O (30 ml) was added. The separated aqueous phase was extracted with Et$_2$O (2×20 ml) and the organic layers collected, dried (Na$_2$SO$_4$) and evaporated to dryness giving a pale yellow oil (2130 mg). This product was pure enough to be submitted to the next reaction without chromatographic purification. For the sake of characterization, a sample of the crude reaction mixture (82 mg) was purified by flash chromatography (hexanes/EtOAc 65:35) to give a diastereomeric mixture of **9** as a colourless oil (60 mg, 91%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.42 (s, 5H), 1.48 (s, 3H), 1.70–1.92 (m, 1H), 2.02–2.22 (m, 2H), 2.28–2.46 (m, 2H), 2.69 (bs, 0.3H, exchanges with D$_2$O), 2.96 (bs, 0.7H, exchanges with D$_2$O), 3.75 (s, 2H), 3.76 (s, 1H), 4.19 (dd, J=7.6 Hz, J=9.8 Hz, 0.7H), 4.29 (dd, J=8.0 Hz, J=9.4 Hz, 0.3H),4.97–5.15 (m, 2H), 5.32 (d, J=4.2 Hz, 0.3H), 5.44 (d, J=4.5, 0.7H), 5.73–5.89 (m, 1H). ^{13}C NMR (75.4 MHz, CDCl$_3$) (mixture of diastereisomers and conformers) δ 26.7, 27.7, 27.8, 27.9, 28.0, 28.1, 28.2, 28.3, 31.0, 31.9, 32.5, 32.8, 33.5, 34.9, 35.7, 38.3, 40.0, 42.0, 42.7, 43.0, 43.7, 44.0, 44.1, 44.8, 51.9, 52.1, 52.3, 52.6, 57.2, 58.4, 59.9, 80.1, 80.9, 81.0, 81.9, 82.1, 83.6, 84.1, 86.3, 86.7, 116.0, 116.1, 116.8, 117.5, 120.2, 121.0, 130.8, 131.3, 134.4, 135.5, 135.7, 136.0, 149.2, 153.1, 153.5, 154.1, 171.8, 172.8, 173.1, 173.3, 173.7, 174.0, 174.3, 175.3; IR (liquid film) 3465, 1753, 1740, 1696, 1366, 1258, 1199, 1167, 1137 cm^{-1}; MS, *m/e* (rel. intensity) 226 (M$^+$—CO$_2$CH$_3$) (21), 212 (1), 198 (1), 184 (7), 170 (49), 149 (3), 126 (63), 117 (6), 108 (20), 97 (3), 81 (23), 69 (6), 57 (100), 41 (22).

The crude product deriving from the previous reaction (2048 mg) was dissolved in CH$_2$Cl$_2$ (30 ml) and added dropwise by syringe to a CH$_2$Cl$_2$ solution (5 ml) of allyltributyltin (3.72 ml, 12.0 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulphonate (2.76 ml, 12.0 mmol) at −78°C under nitrogen. After stirring for 40 min a saturated aqueous solution of NaHCO$_3$ (30 ml) was added, the organic phase separated, and the aqueous layer extracted with CH$_2$Cl$_2$ (2×30 ml). The organic phases were collected, dried (Na$_2$SO$_4$) and evaporated to dryness giving a pale yellow oil which was chromatographed to afford **4-*trans*** (colourless oil, 998 mg, 56%), **4-*cis*** (colourless oil 332 mg, 19%).

4-*trans*: ^{1}H NMR (300 MHz, CDCl$_3$) (mixture of conformers) δ 1.40 (s, 5.4H), 1.48 (s, 3.6H), 1.72–1.81 (dt, J=3.2 Hz, J=13.5 Hz, 1H), 1.98–2.18 (m, 2H), 3.72 (s, 2H), 3.73 (s, 1H), 3.60–3.73 (m, 0.7H), 3.76–3.83 (m, 0.3H), 4.21 (dd, J=3.5 Hz, J=9.9 Hz, 0.7H), 4.28 (dd, J= 3.3, J=10.0, 0.3H), 4.91–5.12 (m, 4H), 5.57–5.82 (m, 2H). ^{13}C NMR (75.4 MHz, CDCl$_3$) (mixture of conformers) δ 28.2, 28.4, 31.8, 32.9, 37.1, 38.0, 38.4, 40.5, 41.6, 51.8, 51.9, 58.9, 59.3, 62.9, 63.0, 79.8, 80.0, 116.6, 116.7, 117.7, 117.8, 134.3, 134.4, 136.3, 136.4, 153.4, 154.1, 173.2, 173.8; IR (liquid film) 3077, 1753, 1698 cm^{-1}; Elemental analysis for C$_{17}$H$_{27}$NO$_4$: Calculated: C, 65.99; H, 8.80; N, 4.53; Found: C, 66.18; H, 8.83; N, 4.52; MS *m/e* (rel. intensity) 268 (M$^+$—CH$_2$CH=CH$_2$) (12), 208 (4), 194 (4), 168 (100), 150 (3), 108 (10), 88 (2), 81 (11), 68 (4), 57 (47).

4-*cis*: ^{1}H NMR (300 MHz, CDCl$_3$) (mixture of conformers) δ 1.57–1.81 (m, 1H), 2.0–2.17 (m, 1H), 2.17–2.44 (m, 5H), 3.73 (s, 1H), 3.92–4.13 (m, 1H), 4.13–4.32 (m, 1H), 4.95–5.19 (m, 4H), 5.59–5.86 (m, 1.2H), 5.86–6.09 (m, 0.8H); ^{13}C NMR (75.4 MHz, CDCl$_3$) (mixture of conformers) δ 28.2, 28.3, 33.5, 33.6, 33.7, 34.4, 35.0, 35.1, 41.6, 42.3, 51.8, 52.0, 58.6, 59.2, 59.3, 59.7, 79.8, 80.1, 116.0, 116.1, 116.2, 117.7, 117.8, 136.2, 136.3, 153.6, 154.3, 173.5, 173.7; IR (liquid film) 3075, 1735, 1643 cm^{-1}; Elemental analysis for C$_{17}$H$_{27}$NO$_4$: Calculated: C, 65.99; H, 8.80; N, 4.53; Found: C, 66.12; H, 8.83; N, 4.54;

3.1.4. (2*S*,3a*S*,7a*S*) and (2*S*,3a*S*,7a*R*)-2,3,3a,4,7,7a-Hexahydroindole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (12-*cis*, 12-*trans*). To a solution of **4-*trans*** (732 mg, 2.37 mmol) in dry CH$_2$Cl$_2$ (60 ml) under nitrogen was added benzylidene-bis(tricyclohexylphosphine) dichlororuthenium (195 mg, 0.24 mmol). After stirring at room temperature for 30 min, TLC analysis (hexanes/EtOAc 85:15) showed that the reaction had gone to completion. Pb(OAc)$_4$ (160 mg)[14] was added and the solution stirred overnight. The solvent was evaporated and the crude mixture flash chromatographed to give **12-*trans*** (606 mg, 91%). The same procedure was adopted for the conversion of **4-*cis*** (302 mg, 0.98 mmol) into **12-*cis*** (244 mg, 89%).

12-*trans*: ^{1}H NMR (300 MHz, CDCl$_3$) (mixture of conformers) δ 1.40 (s, 5.4H), 1.47 (s, 3.6H), 1.71–2.16 (m, 7H), 2.21–2.34 (m, 1H), 2.34–2.48 (m, 1H), 2.85–2.99 (m, 0.4H), 3.08–3.23 (m, 0.6H), 3.24–3.42 (m, 1H), 3.74 (s, 3H), 4.23–4.38 (m, 1H), 5.67 (s, 2H); ^{13}C NMR (75.4 MHz, CDCl$_3$) (mixture of conformers) δ 28.2, 28.3, 30.2, 30.4, 32.3, 33.1, 34.2, 34.9, 41.3, 42.0, 51.8, 51.9, 59.5, 59.9, 60.0, 60.3, 79.7, 80.1, 125.7, 125.8, 125.9, 126.1, 153.5, 154.6, 173.7, 174.1; IR (liquid film) 3024, 1752, 1707, 1364, 1196, 1178, 1159, 1129 cm^{-1}; Elemental analysis for C$_{15}$H$_{23}$NO$_4$: Calculated: C, 64.04; H, 8.24; N, 4.98; Found: C, 64.10; H, 8.24; N, 4.97; MS *m/e* (rel. intensity) 281 (2), 265 (84), 222 (3), 193 (1), 179 (87), 166 (72), 139 (1), 122 (100), 120 (8), 95(2), 91 (1), 78 (4), 68 (5), 57 (82).

12-*cis*: ^{1}H NMR (300 MHz, CDCl$_3$) (mixture of conformers) δ 1.41 (s, 6 H), 1.47 (s, 3H), 1.64–1.91 (m, 1H), 1.91–2.11 (m, 1H), 2.11–2.48 (m, 4H), 2.48–2.74 (m, 1H), 3.73 (s, 3H), 3.85–4.07 (m, 1H), 4.16–4.38 (m, 1H),5.54–5.72 (m, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) (mixture of conformers) δ 25.6, 25.7, 26.8, 27.1, 28.2, 28.4, 34.3, 34.4, 34.9, 35.2, 51.9, 52.0, 53.2, 53.6, 58.4, 59.0, 79.6, 79.7, 123.2, 123.4, 123.8, 124.1, 153.2, 153.9, 173.4, 173.8; IR (liquid film) 3023, 1747, 1695, 1395, 1365, 1172, 1143, 1106 cm^{-1}; Elemental analysis for $C_{15}H_{23}NO_4$: Calculated: C, 64.04; H, 8.24; N, 4.98; Found: C, 63.97; H, 8.23; N, 4.99.

3.1.5. (2*S*,3a*S*,7a*S*) and (2*S*,3a*S*,7a*R*)-Octahydroindole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (2, 3). To a solution of **12-*trans*** (592 mg, 2.11 mmol) in EtOH (40 ml) was added palladium, 5 wt% on activated carbon (120 mg), and the mixture was hydrogenated in a Parr apparatus under 2 atm of H_2 for 30 h. The suspension was filtered on Celite and the solvent evaporated to dryness to give **3** (white solid, 566 mg, 95%). The same procedure was adopted for the hydrogenation of **12-*cis*** (213 mg) to **2** (white solid, 202 mg, 94%).

2: $[\alpha]_D^{22}=-32.7$ (c=1.21, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9H), 0.8–2.1 (m, 10H), 2.10 (m, 1H), 3.55 (s, 3H), 3.60 (m, 1H), 4.05 (m, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) (mixture of conformers): δ 20.3, 23.4, 25.6, 27.2, 27.6, 28.0, 28.2, 31.4, 32.2, 36.2, 36.8, 51.6, 51.8, 56.8, 58.5, 59.0; Elemental analysis for $C_{15}H_{25}NO_4$: Calculated: C, 63.58; H, 8.89; N, 4.94; Found: C, 63.38; H, 8.98; N, 4.85; MS (FAB$^+$): M+1=284.

3: $[\alpha]_D^{22}=-94.4$ (c=0.63, $CHCl_3$); m.p. 54.0–54.5°C (*n*-pentane); ^{1}H NMR (300 MHz, $CDCl_3$) (mixture of conformers) δ 1.1–1.34 (m, 4H) 1.41, 1.47 (2s, 9H), 1.37–1.50 (m, 2H), 1.70–1.89 (m, 3H), 2.22–2.32 (m, 1H), 2.63–3.10 (m, 2H), 3.74 (s, 3H), 4.23, 4.29 (2bt, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) (mixture of conformers) δ 24.8, 25.1, 26.1, 28.7, 28.8, 29.8, 31.6, 32.2, 34.6, 35.2, 46.1, 46.8, 52.3, 60.2, 60.5, 63.9, 64.2, 80.1, 154.1, 174.7; IR (nujol) 1755, 1702, 1397, 1365, 1304, 1261, 1168, 1121, 1024, 902, 733 cm^{-1}; Elemental analysis for $C_{15}H_{25}NO_4$: Calculated: C, 63.58; H, 8.89; N, 4.94; Found: C, 63.70; H, 8.90; N, 4.94.

3.1.6. (2*S*,3a*S*,7a*S*)-Octahydroindole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (2). To a solution of **1** (638.8 mg, 2.37 mmol) in DMF (7.9 ml) $KHCO_3$ (474.9 mg, 4.74 mmol) and CH_3I (0.74 ml, 11.86 mmol) were added. The solution was stirred at room temperature overnight, then the solvent was evaporated. The crude product was suspended in H_2O (8 ml), extracted with EtOAc and the collected organic phases were dried over Na_2SO_4, filtered and evaporated. The crude material was purified by flash chromatography (hexane/EtOAc 8:2) yielding 666.5 mg (99%) of **2** as a colourless oil. $[\alpha]_D^{22}=-32.7$ (c=1.21, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.45 (s, 9H), 0.8–2.1 (m, 10H), 2.10 (m, 1H), 3.55 (s, 3H), 3.60 (m, 1H), 4.05 (m, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) (mixture of conformers): δ 20.3, 23.4, 25.6, 27.2, 27.6, 28.0, 28.2, 31.4, 32.2, 36.2, 36.8, 51.6, 51.8, 56.8, 58.5, 59.0; Elemental analysis for $C_{15}H_{25}NO_4$: Calculated: C, 63.58; H, 8.89; N, 4.94; Found: C, 63.38; H, 8.98; N, 4.85; MS (FAB$^+$): M+1=284.

3.1.7. (2*S*,3a*S*,7a*R*,*S*)-7a-Methoxyoctahydroindole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (14). In a water-cooled cell was placed **2** (438.3 mg, 1.55 mmol), dry CH_3CN/MeOH 7:3 (140 ml), Me_4NBF_4 (3.3 g) and $NaHCO_3$ (6.9 g). The stirred solution was electrolysed using a Pt foil anode (9×4 cm) and a Pt wire cathode at a constant current of 120 mA. The reaction progress was determined by removing 1 ml aliquots, evaporating them, transferring the organic material with Et_2O in a clean flask, evaporating the solvent and determining the ratio of reactant methyl ester (3.75 ppm) to product methyl esters (3.8 ppm) by NMR. When the reaction was complete (after passage of 0.19 F/mol) the suspension was filtered over paper washing the filtered solid with Et_2O and evaporating the collected solution. The crude material was dissolved in H_2O (70 ml), extracted with Et_2O and the organic phase dried over Na_2SO_4, filtered and evaporated. The crude was purified by flash chromatography (hexane/EtOAc 8:2) yielding 409.2 mg (84%) of **14** as a colourless oil in an indeterminable diastereoisomeric mixture. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (2s, 9H), 1.0–2.55 (m, 11H) 3.30 (2s, 3H), 3.70 (2s, 3H), 3.85 (m, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 20.3, 20.4, 20.5, 23.2, 23.5, 25.3, 25.5, 25.8, 26.6, 27.0, 28.2, 33.8, 34.5, 39.4, 39.7, 40.6, 41.0, 50.7, 52.1, 52.5, 53.1, 57.7, 58.8; Elemental analysis for $C_{16}H_{27}NO_5$: Calculated: C, 61.32; H, 8.68; N, 4.47; Found: C, 61.58; H, 8.88; N, 4.40; MS (FAB$^+$): M$^+$=313.

3.1.8. (2*S*,3a*S*,7a*R*)-7a-Allyl-octahydroindole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (15). To a solution of **14** (79.4 mg, 0.253 mmol) in dry CH_2Cl_2 (1.3 ml) allyltributyltin (235 μl, 0.759 mmol) was added under argon atmosphere. This solution was added dropwise to a solution of $BF_3\cdot Et_2O$ (128 μl, 1.012 mmol) in dry CH_2Cl_2 (1.2 ml) at −78°C and stirred at this temperature for 1 h, then warmed to −20°C. A phosphate buffer solution (2.5 ml) was added and the aqueous phase was extracted with CH_2Cl_2. The collected organic phases were dried over Na_2SO_4, filtered and evaporated. The crude material was purified by flash chromatography (hexane/EtOAc 9:1) affording 79.8 mg (97%) of **15** (only 7a*R*-isomer) as a colourless oil. $[\alpha]_D^{22}=+26.9$ (c=1.10, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.40 (s, 9H), 1.20–2.55 (m, 11H), 2.65–3.0 (m, 2H), 3.70 (s, 3H), 3.85 (m, 1H), 5.10 (m, 2H), 5.85 (m, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) (mixture of conformers): δ 20.6, 23.5, 23.8, 25.7, 25.9, 26.0, 26.9, 28.4, 33.9, 34.9, 37.7, 39.3, 39.4, 40.3, 52.0, 58.7, 67.3, 67.6, 79.2, 79.8, 117.9, 118.1, 133.8, 134.2, 153.0, 173.4, 173.8; Elemental analysis for $C_{18}H_{29}NO_4$: Calculated: C, 66.84; H, 9.04; N, 4.33; Found: C, 66.61; H, 8.95; N, 4.25; MS (FAB$^+$): M+1=324.

3.1.9. (2*S*,3a*S*,7a*R*)-7a-Allyl-octahydroindole-1,2-dicarboxylic acid 1-benzyl ester 2-*tert*-butyl ester (16). To a solution of **15** (412.0 mg, 1.27 mmol) in CH_2Cl_2 (12.7 ml) CF_3COOH (4.9 ml, 63.5 mmol) was added dropwise and the solution was stirred at room temperature for 1 h. The solvent was evaporated under reduced pressure, the residue was dissolved in a saturated $NaHCO_3$ solution (13 ml), extracted with CH_2Cl_2 and the collected organic phases were dried over Na_2SO_4, filtered and evaporated. The crude material was purified by flash chromatography (hexane/EtOAc 1:1) affording 251.4 mg (89%) of N-deprotected octahydroindole derivative as a colourless oil. $[\alpha]_D^{22}=-82.7$ (c=1.10, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.10–2.20 (m, 11H), 2.45 (ddd, 2H, J=17 Hz, J=8.8 Hz, J=6.6 Hz), 3.25 (dd, 1H, J=8 Hz, J=4 Hz) 3.70 (s, 3H), 3.90 (s, 1H), 5.05 (m, 2H), 5.75 (m, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 21.4, 22.8, 26.4, 27.5, 37.8, 40.8, 45.3, 52.4, 57.8, 68.3, 118.2, 133.5, 177.1; Elemental analysis for $C_{13}H_{21}NO_2$: Calculated: C, 69.92; H, 9.48; N, 6.27; Found: C, 69.81; H, 9.26; N, 6.08; MS (FAB$^+$): M^+=223.

The previous compound (251.4 mg, 1.12 mmol) was dissolved in EtOAc/H_2O 1:1 (11.2 ml) and $KHCO_3$ (224.3 mg, 2.24 mmol) and benzyl chloroformate (174 μl, 1.23 mmol) were added. The reaction was stirred vigorously for 2 h, then the phases were separated and the aqueous layer was washed with EtOAc. The combined organic phases were dried over Na_2SO_4, filtered and evaporated. The crude product was purified by flash column chromatography (hexane/EtOAc 9:1) to provide the *N*-benzyloxy derivative as a colourless oil (396.1 mg, 99% yield). $[\alpha]_D^{22}=+18.8$ (c=1.21, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) (mixture of conformers): δ 1.0–2.5 (m, 22H), 2.65–3.10 (m, 4H), 3.50 (s, 3H), 3.70 (s, 3H), 3.90 (m, 2H), 4.95–5.15 (m, 8H), 5.85 (m, 2H), 7.20–7.40 (m, 10H); ^{13}C NMR (50.3 MHz, $CDCl_3$) (mixture of conformers): δ 20.3, 20.4, 23.3, 23.4, 24.6, 25.5, 25.6, 25.9, 33.9, 34.8, 37.6, 38.8, 39.1, 40.7, 52.1, 52.3, 58.5, 59.2, 66.4, 66.7, 67.4, 68.0, 118.1, 127.6, 127.7, 127.8, 128.0, 128.3, 133.9, 134.1, 136.4, 136.9, 153.5, 153.6, 174.7; Elemental analysis for $C_{21}H_{27}NO_4$: Calculated: C, 70.56; H, 7.61; N, 3.92; Found: C, 70.32; H, 7.80; N, 4.01; MS (FAB$^+$): M^+357.

To a solution of *N*-benzyloxy derivative (61.0 mg, 0.170 mmol) in dioxane (1.7 ml) a 2N solution of LiOH (0.42 ml, 0.85 mmol) was added and the solution was stirred at 50°C for 2 days. The solvent was evaporated, the residue was dissolved in a 1 M solution of NaH_2PO_4 (1.7 ml) and extracted with EtOAc. The organic phases were dried (Na_2SO_4), filtered and evaporated affording the corresponding acid (58.4 mg, 100%), as a yellowish solid, that was submitted to the next reaction without further purification. ^1H NMR (200 MHz, $CDCl_3$): δ 1.05–2.5 (m, 11H), 2.65–3.10 (ddd, 2H, J=15 Hz, J=8.8 Hz, J=6.6 Hz), 4.0 (m, 1H) 5.0–5.20 (m, 4H), 5.85 (m, 1H), 7.20–7.40 (m, 5H), 11.5 (bs, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) (mixture of conformers): δ 20.2, 20.4, 23.4, 23.6, 25.5, 25.9, 27.2, 34.0, 34.6, 37.2, 38.9, 39.1, 40.3, 58.9, 59.3, 66.9, 67.2, 68.3, 118.4, 118.6, 127.6, 127.7, 127.8, 128.0, 128.3, 128.4, 133.4, 133.7, 136.2, 136.5, 153.6, 154.6, 178.8, 180.3; MS (FAB$^+$): M+1=344.

The acid (380.5 mg, 1.11 mmol) was dissolved in dry benzene (11 ml) and *N*,*N*-dimethylformamide di-*tert*-butyl acetal (1.3 ml, 5.55 mmol) was added dropwise, the reaction was refluxed for 1 h then $Me_2NCH(OtBu)_2$ (1.3 ml) was added dropwise and the reaction was heated for 2 h, then H_2O (11 ml) was added. The phases were separated and the aqueous layer was washed with EtOAc. The collected organic phases were dried over Na_2SO_4, filtered and evaporated. The crude residue was purified by flash chromatography (hexane/EtOAc 9:1) yielding 409.9 mg (92%) of **16** as a colourless oil. $[\alpha]_D^{22}=+4.0$ (c=1.11, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) (mixture of conformers): δ 1.10–2.55 (m, 22H), 1.38 (s, 9H), 1.47 (s, 9H), 2.60–3.10 (m, 4H), 3.90 (m, 2H), 4.95–5.30 (m, 8H), 5.90 (m, 2H), 7.20–7.40 (m, 10H); ^{13}C NMR (50.3 MHz, $CDCl_3$) (mixture of conformers): δ 20.4, 20.6, 23.4, 23.6, 25.5, 25.6, 25.9, 26.9, 27.7, 33.8, 34.7, 37.3, 39.1, 40.5, 58.5, 59.3, 66.2, 66.7, 67.8, 68.4, 80.8, 80.9, 117.6, 117.9, 127.6, 127.7, 127.9, 128.2, 134.2, 134.6, 136.3, 137.1, 153.6, 172.9, 173.0; Elemental analysis for $C_{24}H_{33}NO_4$: Calculated: C, 72.15; H, 8.33; N, 3.51; Found: C, 72.29; H, 8.12; N, 3.62; MS (FAB$^+$): M+1=400.

3.1.10. (2*S*,3a*S*,7a*R*)-7a-(2-Oxoethyl)-octahydroindole-1,2-dicarboxylic acid 1-benzyl ester 2-*tert*-butyl ester (17). To a solution of **16** (406.5 mg, 1.017 mmol) in acetone/water 8:1 (10 ml) $OsCl_3$ (29.6 mg) and $Me_3NO\cdot 2H_2O$ (226.0 mg, 2.034 mmol) were added. The solution was stirred at room temperature for 2 h, then $NaIO_4$ (543.8 mg, 2.54 mmol) was added and stirred for 2 h. The solvent was evaporated, the residue was dissolved in water and extracted with EtOAc. The combined organic phases were dried (Na_2SO_4), filtered and evaporated. The crude material was purified by flash chromatography (hexane/EtOAc 9:1) affording **17** (380.8 mg, 93%) as a colourless oil. $[\alpha]_D^{22}=-22.1$ (c=0.96, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) (mixture of conformers): δ 1.10–2.55 (m, 22H), 1.39 (s, 9H), 1.43 (s, 9H), 2.65–3.25 (m, 4H), 3.80 (m, 1H), 3.93 (m, 1H), 5.0–5.30 (m, 4H), 7.35 (m, 10H), 9.70 (m, 1H), 9.88 (m, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) (mixture of conformers): δ 20.4, 20.6, 23.5, 25.3, 25.4, 26.8, 27.5, 33.9, 34.9, 37.5, 48.3, 58.0, 58.8, 66.6, 67.0, 127.8, 128.0, 128.3, 199.2, 199.6; Elemental analysis for $C_{23}H_{31}NO_5$: Calculated: C, 68.80; H, 7.78; N, 3.49; Found: C, 68.95; H, 7.77; N, 3.69; MS (FAB$^+$): M+1=402.

3.1.11. (2*S*,3a*S*,7a*R*)-7a-(3-Benzyloxycarbonylamino-3-methoxycarbonyl-allyl)-octahydroindole-1,2-dicarboxylic acid 1-benzyl ester 2-*tert*-butyl ester (18). To a stirred mixture of *t*BuOK (17.6 mg, 0.157 mmol) in 0.4 ml of dry CH_2Cl_2 under nitrogen atmosphere, at −78°C, was added a solution of *Z*-(α)-phosphonoglycine trimethyl ester (52.2 mg, 0.157 mmol) in 0.4 ml of dry CH_2Cl_2. The solution was stirred for 30 min at this temperature and then a solution of aldehyde **17** (42.0 mg, 0.105 mmol) in dry CH_2Cl_2 (0.5 ml) was added. The solution was stirred for 1 h at −78°C, then warmed to room temperature and stirred overnight. A phosphate buffer (1.3 ml) was added and the aqueous phase was extracted with CH_2Cl_2, dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The crude material was purified by flash chromatography (hexane/EtOAc 8:2), affording 54.1 mg (85%) of acrylic ester **18** (1:1.5 *E*/*Z* ratio) as a colourless oil. ^1H NMR (300 MHz, $CDCl_3$, 323 K) (*Z*/*E* mixture) (mixture of conformers): δ 1.32, 1.35, 1.43, 1.46 (4s, 18H), 1.1–2.6 (m, 22H), 3.0 (m, 4H), 3.65, 3.70, 3.72, 3.75 (4s, 6H), 3.85–3.95 (m, 2H), 5.0–5.2 (m, 8H), 6.5 (bs, 0.8H), 6.6 (t, 1.2H, J=7.8 Hz), 6.7 (bs, 1.2H), 6.8 (t, 0.8H, J=7.8 Hz), 7.2–7.4 (m, 20H); ^{13}C NMR (50.3 MHz, $CDCl_3$) (*Z*/*E* mixture) (mixture of conformers): δ 20.5, 20.6, 20.7, 23.5, 23.7, 25.5, 25.7, 26.0, 26.9, 27.0, 27.8, 28.3, 29.7, 30.0, 30.3, 33.4, 33.8, 34.0, 34.3, 34.5, 34.7, 34.9, 35.3, 37.4, 37.8, 38.9, 52.3, 58.6, 58.7, 59.3, 66.4, 66.7, 66.9, 67.2, 67.4, 68.0, 68.5, 68.9, 81.8, 125.5, 127.8, 128.0, 128.2, 128.4, 128.5, 132.2, 133.4, 136.1, 136.9, 153.8, 154.2, 154.3, 165.1, 172.5; Elemental analysis for $C_{34}H_{42}N_2O_8$: Calculated: C, 67.31; H, 6.98; N, 4.61; Found: C, 67.55; H, 7.02; N, 4.49; MS (FAB$^+$): M+1=607.

3.1.12. (2*S*,3a*S*,7a*R*)-7a-[3-(*N*-Benzyloxycarbonyl-*N*′-*tert*-butoxycarbonylamino)-3-methoxycarbonyl-allyl]-octahydroindole-1,2-dicarboxylic acid 1-benzyl ester 2-*tert*-butyl ester (19). A solution of **18** (45.2 mg, 0.074 mmol), $(Boc)_2O$ (32.5 mg, 0.149 mmol) and a catalytic quantity of DMAP in 0.8 ml of dry THF, was stirred for 2 h under nitrogen. The solution was then quenched with water (0.8 ml) and extracted with ethyl acetate. The organic phase was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude material was purified by flash chromatography (hexane/EtOAc 8:2), yielding 46.0 mg (88%) of **19** as a sticky solid.

^{1}H NMR (200 MHz, $CDCl_3$) (*Z*/*E* mixture) (mixture of conformers): δ 1.32, 1.42 (2s, 36H), 1.0–3.0 (m, 26H), 3.62, 3.68 (2s, 6H), 3.75–3.95 (m, 2H), 4.9–5.3 (m, 8H), 6.4 (m, 0.8H), 7.0 (m, 1.2H), 7.2–7.4 (m, 20H); ^{13}C NMR (50.3 MHz, $CDCl_3$) (*Z*/*E* mixture) (mixture of conformers): δ 20.5, 23.6, 25.6, 26.9, 27.7, 33.4, 35.0, 52.1, 58.4, 59.4, 66.6, 67.0, 68.3, 76.3, 76.9, 77.6, 127.8, 128.4, 139.2, 143.0; Elemental analysis for $C_{39}H_{50}N_2O_{10}$: Calculated: C, 66.27; H, 7.13; N, 3.96; Found: C, 66.45; H, 7.05; N, 4.12; MS (FAB$^+$): M+Na=729.

3.1.13. (3*S*,6*S*,7a*S*,11a*R*) and (3*R*,6*S*,7a*S*,11a*R*)-3-*tert*-Butoxycarbonylamino-4-oxodecahydropyrido [2,1-*i*]-indole-6-carboxylic acid *tert*-butyl ester (20, 21). A solution of **19** (95.2 mg, 0.134 mmol) and a catalytic quantity of 10% Pd—C in 1.3 ml of MeOH was stirred under H_2 overnight. The catalyst was then filtered through celite and the filtration bed was washed with MeOH. The solvent was evaporated under reduced pressure, the residue was dissolved in toluene (13 ml) and refluxed for 48 h. The solvent was removed and the two diastereoisomers formed were separated by flash chromatography (hexane/EtOAc 6:4), yielding 23.0 mg of **20** and 23.4 mg of **21** (85%) (1:1 diastereoisomeric ratio) as sticky solids.

20: $[\alpha]_D^{22}=+22.6$ (c=0.97, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13–1.37 (3H), 1.44 and 1.52 (2s, 18H), 1.38–1.55 (2H), 1.57–1.72 (4H), 1.88–2.00 (2H), 2.22–2.37 (2H), 2.47 (m, 1H), 2.56 (m, 1H), 3.95 (m, 1H), 4.32 (m, 1H), 5.68 (bs, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 20.4, 23.4, 25.2, 25.8, 26.4, 27.7, 28.3, 30.2, 34.2, 40.4, 48.2, 57.6, 67.4, 79.2, 82.2, 172.8; Elemental analysis for $C_{22}H_{36}N_2O_5$: Calculated: C, 64.68; H, 8.88; N, 6.85; Found: C, 64.74; H, 8.78; N, 6.49; MS (FAB$^+$): M+1=409.

21: $[\alpha]_D^{22}=+22.8$ (c=1.05, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05–1.35 (5H), 1.44 and 1.49 (2s, 18H), 1.52–1.70 (3H), 1.78 (m, 1H), 1.90–2.10 (2H), 2.12–2.30 (2H), 2.32–2.52 (2H), 4.10 (m, 1H), 4.18 (m, 1H), 5.14 (bs, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$: δ 20.1, 23.0, 25.2, 25.8, 27.1, 27.8, 28.2, 32.9, 34.6, 38.9, 50.9, 58.4, 67.7, 79.4, 82.2, 167.4, 174.1; Elemental analysis for $C_{22}H_{36}N_2O_5$: Calculated: C, 64.68; H, 8.88; N, 6.85; Found: C, 64.46; H, 8.96; N, 6.45; MS (FAB$^+$): M+1=409.

Acknowledgements

The authors thank *CNR* and *MURST* (*COFIN 2000*, “*Sintesi di Mimetici e Analoghi di Sostanze Naturali Biologicamente Attive*”) for financial support, and Dr. E. Milano and Dr. V. Vinci for their valuable assistance.

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